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Health and Environmental Effects Profile for 2-Chloro-1,3-Butadiene

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 2-CHLORO-1,3-BUTADIENE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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EXECUTIVE SUMMARY

Very little information is available in the literature pertaining to the fate and transport processes of chloroprene in the environment. In the atmosphere, probably the most important fate-determining process of this chemical is its reaction with ozone. The atmospheric half-life for this reaction has been estimated to be 2 hours. In water bodies, evaporation and oxidation by singlet oxygen may be the most significant fate determining processes. For lack of monitoring data, the human intake of this chemical from drinking water, foods and skin exposure cannot be estimated. Until more ambient air monitoring data are available, it is impossible to estimate the human intake of chloroprene through inhalation.

Chloroprene has been shown to be mutagenic in bacterial systems and experimental animals *in vivo*, and clastogenic in occupationally exposed humans. Epidemiological data indicate that occupational exposure to chloroprene may be linked to increased incidence of lung and skin cancer; however, all the studies had major methodological deficiencies.

Repeated exposure to chloroprene results in central nervous system, cardiovascular and reproductive abnormalities. Acute effects of chloroprene exposure include central nervous system depression, lung injury, liver and kidney damage, irritation of the skin and mucous membranes, respiratory difficulties, dermatitis and alopecia.

An ADI of 0.013 mg/day has been estimated from inhalation exposures based upon the National Institute for Occupational Safety and Health's (NIOSH) recommended 15-minute ceiling concentration for work-place exposures of 1 ppm chloroprene.

Pertinent data regarding the aquatic toxicity of chloroprene were not located in the available literature.

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16. ABSTRACT

The Health and Environmental Effects Profile for 2-Chloro-1,3-Butadiene was prepared by the Office of Health and Environmental Assessment, Environmental Criteria Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potenial human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 2-Chloro-1,3-Butadiene has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for 2 Chloro-1,3-Butadiene is 1.9×10^{-3} mg/kg bw/day for oral exposure.

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1. INTRODUCTION

2-Chloro-1,3-butadiene (chloroprene) is a colorless, mobile, volatile liquid (Johnson, 1979). Chloroprene is manufactured in a three step process: 1) chlorination of 1,3-butadiene to form 1,4-dichloro-2-butene, 2) isomerization to 1,2-dichloro-3-butene and 3) dehydrochlorination with caustic soda to form 2-chloro-1,3-butadiene.

CAS Registry Number	126-99-8
Formula	C_4H_5Cl
Molecular Weight	88.54 (Johnson, 1979)
Melting Point	-130°C (Johnson, 1979)
Boiling Point	59.4°C (Johnson, 1979)
Density	at 20°C:0.9585 g/mℓ (Johnson, 1979)
Flash Point	-20°C (ASTM, open cup) (Johnson, 1979)
Vapor Pressure	215.4 mm at 25°C (Torkelson and Rowe, 1981)
Solubility in water (calculated)	5400 mg/ℓ (Mabey et al., 1982)
Log octanol-water partition coefficient (calculated)	1.78 (Mabey et al., 1982)

In 1976, two United States companies produced an estimated 164 million kg of chloroprene, and the total world production in 1977 was estimated at 300 million kg (IARC, 1979).

Virtually all chloroprene is polymerized to form polychloroprene, a synthetic rubber used for wire and cable covers, gaskets, automotive parts, adhesives, caulks, flame-resistant cushioning and other applications requiring chemical, oil and weather resistance or high gum strength (Johnson, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Very little information is available in the literature pertaining to the fate and transport processes of chloroprene in the environment. In the atmosphere, chloroprene is very slightly reactive towards $RO_2\cdot$ radicals. The half-life for this reaction has been estimated to be 2.2 years (Brown et al., 1975). The chemical is more reactive towards atmospheric OH· radicals and O_3. The half-lives for these reactions have been estimated to be 21 hours and 2 hours, respectively (Brown et al., 1975). The reaction of chloroprene with O_3 is expected to yield 2-chloroacrolein as the product (Brown et al., 1975). The experimental persistence data for chloroprene with regard to volatilization and chemical reactions in aquatic media could not be found in the available literature. However, some theoretical predictions about the aquatic fate and transport of chloroprene can be made. Based on the vapor pressure and solubility data presented earlier, the Henry's constant for this compound can be estimated to be 4.6×10^{-3} atm. m^3/mol (MacKay and Wolkoff, 1973). Thus, the value of Henry's constant for chloroprene is close to that of benzene (5.5×10^{-3} atm. m^3/mol) as given by Mackay and Leinonen (1975). The estimated evaporative half-life for benzene from 1 meter depth of water is ~5 hours. (Mackay and Leinonen, 1975). Chloroprene is also expected to evaporate quite rapidly from aquatic media, particularly in turbulent water bodies.

The sediment sorption partition coefficient for chloroprene from aquatic media can be calculated to be 0.3 in sediments containing 0.5% organic carbon by the correlation equation of Schwarzenbach and Westall (1981), and an octanol/water partition log coefficient (log K_{ow}) value of 1.78 (Mabey et al., 1982). The log K_{oc} value for this compound in such sediments would be 1.78 using a second equation from these authors. This log K_{oc} value is

slightly less than the experimental log K_{oc} value of 1.92 for benzene (Schwarzenbach and Westall, 1981). Therefore, the transport of chloroprene from aquatic phase to sediments is expected to be less than that expected for benzene.

Chloroprene is not expected to undergo photolysis in aquatic media (Mabey et al., 1982).* Oxidation of this compound by peroxy radicals is not expected to be a significant process from the estimated rate constant value ($2\ M^{-1}\ sec^{-1}$) (Mabey et al., 1982) and the estimated concentration of peroxy radicals of 10^{-9} M in aquatic media (Mill and Mabey, 1980). However, the oxidation of chloroprene in aquatic media by singlet oxygen can be estimated to be <1 day from the estimated rate constant value of $10^{7}\ M^{-1}\ sec^{-1}$ (Mabey et al., 1982) and the estimated concentration of 10^{-12} M (Mill and Mabey, 1980). Therefore, this reaction may be a significant fate determining process for chloroprene in aquatic media. No prediction regarding chemical oxidation in soils can be made at the present time.

No experimental information was found regarding the microbial degradability of chloroprene in aquatic environment or soils. Assuming the estimated microbial degradation rate constant of 10^{-10} mℓ $cell^{-1}$ $hour^{-1}$ (Mabey et al., 1982) and the concentration of microorganisms in aquatic media as $5x10^{5}$ cell $mℓ^{-1}$ (Burns et al., 1981), biodegradation of this compound in aquatic phase does not appear to be a significant fate process.

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*Mabey et al (1982) caution that their estimated rate constants and calculated physical parameters were intended only for use in preliminary assessments to determine relative contributions of potential degradation or dissipation mechanisms, and should not be used for determining absolute rates without further consulations with the authors.

No prediction regarding microbial degradability of this chemical in soils can be made at the present time. Based on the estimated log K_{oc} value, the leaching and volatility of the compound from soil is expected to follow a pattern similar to that of benzene.

3. EXPOSURE

3.1. WATER

Although chloroprene or its isomer has been detected at ~1 ppb level in the Ohio River near Cannelton, Indiana and Houston Ship Channel near Pasadena Gardens, Texas (Ewing et al., 1977), its detection in any drinking water is rare. However, its detection (no quantitative value) in an unspecified United States drinking water has been reported (NAS, 1977).

3.2. FOOD

The U.S. Food and Drug Administration (FDA) permits the use of polymers of chloroprene as a component of adhesives that are intended for use in food packaging (IARC, 1979). However, no data indicating its level in foods could be found.

3.3. AIR

During 1973, the airborne concentrations of chloroprene in a United States chloroprene polymerization plant were found to range from 50-5000 mg/m^3 in the make-up area, from 440-24,300 mg/m^3 in the reactor area, from 10-1500 mg/m^3 in the monomer recovery area, and from 400-900 mg/m^3 in the latex area (IARC, 1979). In 1977, mean airborne concentrations of chloroprene of up to 0.72 mg/m^3 were reported in a roll building area in a metal fabricating plant where polychloroprene was applied extensively to metal cylinders prior to vulcanization (IARC, 1979). It has been estimated that ~2500-3000 workers in the United States are currently exposed to chloroprene during its manufacture and polymerization (IARC, 1979).

Chloroprene concentration in air in the immediate vicinity of a polychloroprene rubber plant in Russia was 28.5 mg/m^3. At distances of 500 and 7000 meters away from the plant, the chloroprene concentrations were 0.73 and 0.2 mg/m^3, respectively (IARC, 1979). The ambient air concentra-

tion of chloroprene in Baton Rouge, Louisiana, was monitored by Hughes et al. (1980) and no chloroprene could be detected. However, Harkov et al. (1980) monitored the ambient air throughout New Jersey and found that chloroprene was ubiquitous throughout the state at concentrations <1 ppb. A recent report (Brodzinsky and Singh, 1982) summarized the ambient air concentrations of organics from both urban/suburban and source areas in the United States. Out of 19 source areas monitored, only two showed detectable levels of chloroprene. The mean concentration of chloroprene in these two sources has been reported to be 0.6 ppb.

3.4. DERMAL

Pertinent data regarding dermal exposure to chloroprene were not located in the available literature.

4. PHARMACOKINETICS

Although the metabolism of chloroprene has not been thoroughly investigated, it has been hypothesized that chloroprene is metabolized in a manner similar to vinyl chloride (Haley, 1978). This implies that chloroprene would be first metabolized to a reactive epoxide intermediate via hepatic mixed function oxidases. This intermediate could then give rise to an aldehyde or undergo conjugation with glutathione. According to Haley (1978), limited available data support this hypothesis. Alternatively, studies from the Russian literature reviewed by Haley (1978) have shown that chloroprene forms peroxides in vitro taking up oxygen in positions 1 and 2. Bartsch et al. (1976) have shown that mutagenicity in Salmonella is appreciably enhanced by addition of a hepatic microsomal fraction, suggesting formation of a reactive intermediate.

The involvement of glutathione has been somewhat more thoroughly studied. Summer and Greim (1980) have shown in SPF Wistar rats that following a single oral dose of chloroprene (100 or 200 mg/kg), there is a rapid decrease in hepatic GSH to 55 and 39%, respectively, of the control value by 3 hours post-treatment. In Cophen A-50 pretreated animals, the decrease was 57 and 55%, respectively. In isolated hepatocytes, cellular GSH decreased to 50% of control levels within 15 minutes of addition of 3 mM chloroprene. Oral dosing of SPF Wistar rats with chloroprene resulted in a dose-related increase in urinary excretion of thioethers (presumably GSH-conjugates and mercapturic acids) in the urine. At high doses, a decline in excretion was observed, possibly due to GSH depletion.

Jaeger et al. (1975) found that fasted rats were more sensitive to inhalation effects of chloroprene, both as indicated by lethality and as shown

by increases in serum alanine α ketoglutarate transaminase (AKT) (an indicator of hepatotoxicity). Rats were exposed for 4 hours to 500, 1000, 2000 or 10,000 ppm chloroprene. At concentrations <10,000 ppm, effects on serum AKT and survival were seen only in fasted rats. These authors present evidence that the reported differences in toxicity are related to hepatic glutathione levels.

5. EFFECTS

5.1. CARCINOGENICITY

Although some epidemioligical data suggest that occupational exposure to chloroprene may be associated with increased incidence of lung and skin cancer, all such studies have major methodological deficiencies. Animal as well as some epidemiology data on chloroprene's possible carcinogenicity are negative.

5.1.1. Human Studies. Khachatrian (1972a) reported data on skin cancer incidence in chloroprene workers. Exposure concentrations were not reported. Cases were followed from 1956-1970, and incidence rates were reported for chloroprene workers, chemical workers, non-chemical workers and non-industrial workers. However, IARC (1979) notes that this study failed to distinguish prevalent from incident cases, failed to document completeness of case reporting among the exposure groups, failed to adjust for age and sex, and failed to control for the effects of smoking and exposure to other toxicants. In addition, absence of histological information on all types of reported cancers is stressed as a serious limitation.

In a simultaneous study, Khachatrian (1972b) reported the incidence of lung cancer in chloroprene workers, also from the period of 1956-1970. Of the 87 lung cancer cases, 16 were also identified as former chromium workers. Again, exposure levels were not reported. Seventy-six percent of the workers with lung cancer had chronic bronchitis, 3.4% had tuberculosis, and 4.5% had pneumonia; 66% of the workers with lung cancer smoked. NIOSH (1977) notes that the methods used for cancer diagnosis were not specified, and that there were inconsistencies between data reported in the text versus the tables. Moreover, NIOSH (1977) notes that a panel of Soviet experts has determined that there were methodological errors that could lead to in-

correct conclusions. IARC (1979) emphasizes that the limitations associated with the skin cancer study also apply to the lung cancer study.

Pell (1976) examined cancer mortality in two populations of chloroprene workers. One population (234 men) was first exposed between 1931 and 1948; these individuals were followed from 1956-1974. The second population (1576 men) was first exposed between 1942 and 1957, and the men were followed from 1957-1974. The number of lung cancer deaths did not differ from that expected; the risks of digestive cancer, and lymphatic and hematopoietic cancer were slightly elevated in the second cohort (19 vs. 13.3 expected, and 7 vs. 4.5 expected, respectively). There were eight lung cancer cases among maintenance mechanics in the second cohort (40% of total lung cancers), although maintenance mechanics accounted for only 17% of the population. These workers would be expected to have a high exposure to chloroprene. IARC (1979) notes the following limitations in this study: retired, disabled and former workers were not uniformly included; smoking and exposure to other toxicants were not considered; exposure concentrations were lacking; data on cell types of the cancers were not reported; and the second cohort was not followed for an adequate latency period. Skin cancer incidence was not considered.

5.1.2. Experimental Animals. Ponomarkov and Tomatis (1980) administered 100 mg/kg chloroprene in olive oil to BDIV rats. A single dose was given to pregnant dams (24 animals) by stomach tube on day 17 of gestation. Progeny (81 males, 64 females) were treated weekly from weaning with 50 mg/kg chloroprene for 120 weeks. Fourteen pregnant dams receiving 0.3 mℓ olive oil on day 17 of gestation served as controls. Of their offspring, 53 males and 53 females received weekly doses of 0.3 mℓ olive oil from weaning for

120 weeks. After 120 weeks of treatment, all surviving animals were autopsied. All "major" internal organs, in addition to those which showed gross abnormalities, were examined histologically. No differences in survival or body weights were found between treated animals and controls. Animals receiving chloroprene that died within the first 23-35 weeks showed severe congestion of the lungs and kidneys. In some of the animals autopsied following 80-90 weeks of treatment, severe liver necrosis was observed. The incidence of tumors in chloroprene treated rats was the same as that observed in vehicle treated controls.

Zil'fyan et al. (1975, 1977) administered 200 mg/kg chloroprene in sunflower oil by gavage to 100 rats 2 times/week for 25 weeks. Forty rats survived for 2 years. Tumors related to treatment were not observed.

The same group (Zil'fyan et al., 1975, 1977) applied chloroprene, 9,10-dimethyl-1,2-benzanthracene (DMBA), or both to the shaved skin of mice. A 50% solution of chloroprene in benzene was applied 2 times/week for 25 weeks to 100 mice. A 0.1% solution of DMBA in benzene was applied using the same exposure regimen (80 mice). In addition, 50 applications of the 50% chloroprene solution were combined with five applications of 0.01% DMBA (80 mice). Of the mice treated with 0.1% DMBA, 92% developed skin carcinomas. Skin tumors were not found in the other two groups.

In another segment of this group's evaluation (Zil'fyan et al., 1977), 100 rats received 200 mg/kg chloroprene intratracheally. Animals were dosed every 20 days until a total of five treatments was achieved. Gross and microscopic evaluation of the lungs of animals that died or were sacrificed 6 or 14 months after exposure did not reveal any tumors.

Zil'fyan et al. (1977) administered 10 subcutaneous injections of 400 mg/kg chloroprene in sunflower oil to 110 rats, and an additional 100

rats received 50 injections of 200 mg/kg. In the first group, 88 animals survived >6 months and, in the second group, there were 46 survivors. No local sarcomas were reported in either group within the 2-year observation period. Of 60 rats injected with a single dose of 0.5 mg DMBA, 50 survived until the appearance of the first tumor (3.5 months), and 32 developed local sarcomas. An additional group of animals received 5 mg DMBA as well as 50 injections of 200 mg/kg chloroprene; 42 rats survived until the appearance of the first tumor (4 months), and 24 developed local sarcomas.

ACGIH (1980) cite unpublished data which indicate a lack of carcinogenic effect in rats or hamsters exposed to 50 ppm chloroprene for 2 years or 18 months. Growth retardation was noted. Exposure to 10 ppm did not result in any observable adverse effects.

5.2. MUTAGENICITY

5.2.1. Human Studies. The original Russian articles quoted in this section were unavailable for analysis. Information was obtained from IARC (1979).

Katosova (1973) reported a significant elevation in incidence of chromosome aberrations in blood cells from 18 workers exposed to an average concentration of 18 mg/m^3 chloroprene. Workers were exposed from 2-10 years. A frequency of 4.7% aberrations and 3.7% gaps was reported for the chloroprene exposed group, as compared to 0.65 and 1.14%, respectively, in a group of nine non-chloroprene exposed auto workers. There was no correlation between exposure time and frequency of aberrations.

Zhurkov et al. (1977) evaluated 56 workers exposed to chloroprene, chloroprene latex or chloroprene rubber (average chloroprene air concentration of 6 mg/m^3). The frequency of chromosome aberrations in cultured lymphocytes from these workers was 2.78%. Reported aberration frequencies for two control groups were 0.53 and 1.14%.

Fomenko and Katosova (1973) reported an increased incidence of chromosome aberrations in lymphocytes from 28 workers exposed for 1-20 years to average chloroprene concentrations of 1-7 mg/m³. A major deficiency in this study, however, is the use of spontaneous control data for cultured lymphocytes from another independent study. Thus, the small increases in chromosomal aberrations observed may be misleading.

Bagramyan et al. (1976) evaluated chromosome aberrations in lymphocytes from five workers exposed to 2-2.2 mg/m³ chloroprene, in combination with 0.5-2 mg/m³ methyl methacrylate. The incidence of chromatid breaks was 16.8%, and the incidence of chromosome breaks was 16.9%.

Gu (1981) found that the rate of sister chromatid exchange (SCE) in lymphocytes from chloroprene exposed workers was not significantly different from controls, nor did chloroprene induce SCE in vitro.

5.2.2. In Vivo Tests with Experimental Animals. The number of dominant lethal mutations was increased when rats were exposed to 0.14 mg/m³ chloroprene for 2.5 months, but not following exposure to 0.057 mg/m³. In mice, exposure for 2 months to chloroprene concentrations of 3.5 and 1.85 mg/m³ increased the number of dominant lethal mutations. Exposure to concentrations of 0.05, 0.064, 0.13 and 0.32 mg/m³ had no significant effect. Chromosome aberrations in bone marrow were elevated in mice exposed to 0.13, 0.32, 1.85 or 3.5 mg/m³ chloroprene for 2 months, but not in groups exposed to 0.064 or 0.054 mg/m³ (Sanotskii, 1976).

5.2.3. Other Systems. Drosophila were fed four different concentrations of chloroprene. A dose effect relationship for recessive lethal mutations could not be established. The author pooled the data for all dose levels and found that these pooled data showed a higher incidence of recessive lethal mutations than controls (Vogel, 1979).

Bartsch et al. (1976, 1979) reported that chloroprene was mutagenic to Salmonella typhimurium TA100. Mutagenicity increased by the addition of a microsomal fraction from mouse liver. Mouse kidney also increased mutagenicity, but was only 50% as effective as liver. Phenobarbital pretreatment of animals increased the mutagenic response for both organs. Human liver was active (~33% as effective as mouse liver), but neither mouse nor human lung showed an effect. That dimers or other impurities in chloroprene were responsible for the mutagenic activity was ruled out by the use of highly purified (99.7%) chloroprene which resulted in mutagenicity no different from other experiments with less pure compound.

Drevon and Kuroki (1979) found chloroprene was not mutagenic when tested with V79 Chinese hamster cells. Markovits et al. (1977) found that chloroprene induced transformation in cultured hamster lung cells. Menezes et al. (1979) also found that chloroprene induced transformation in hamster lung cells. In addition, they demonstrated that when hamsters were innoculated intraoccularly with these transformed cells, malignant fibrosarcomas developed.

In summary, the weight of the available evidence suggests that chloroprene is a mutagen. Positive results were obtained in bacteria, Drosophila, mice, rats and perhaps humans. In addition, transformation was induced by chloroprene in cultured hamster lung cells. However, the original data were not available for some of the studies cited, and data on the purity of the samples of chloroprene used in many of the studies were not provided.

5.3. TERATOGENICITY

Culik et al. (1978) exposed pregnant rats to chloroprene via inhalation. Daily exposures were of 4 hours duration and exposure concentrations were 0, 1, 10 and 25 ppm chloroprene. Two studies were conducted. In the first, 50

dams/group were exposed on days 1 through 12 of gestation and sacrificed on day 17 in order to evaluate the embryotoxic potential of chloroprene. In the second, 25 dams/group were exposed on days 3 through 20 of gestation and sacrificed on day 21 to evaluate the teratogenic potential of chloroprene. No effects on embryonic or fetal survival, nor incidence of soft tissue or skeletal defects were demonstrated. These data are at odds with other investigators (V. infra). Culik et al., (1978) attempted to limit exposure to chloroprene per se. However, chloroprene readily polymerizes when exposed to light and heat, and may oxidize to form peroxides as well as other reaction products, some of which may be more toxic than chloroprene. Culik et al. (1978) hypothesize that this may account for the differences between their data and those of other investigators.

Salnikova (1968) evaluated the embryotoxic effects of inhaled combinations of chloroprene and ammonia. The method of generating the vapors and the identity of contaminants were not discussed. The concentration of chloroprene was 14.4 mg/m³ and the concentration of ammonia was 4.8 mg/m³. Thirteen mice and 11 rats were exposed to this mixture for 4 hours/day for the first 18 or 19 days of gestation, respectively. An ammonia control group exposed to 58 mg/m³ was included (10 mice, 7 rats), and a negative control group exposed to air alone (11 mice, 9 rats) was also included. A group exposed solely to chloroprene was not included. Dams were evaluated on day 17 for changes in body weight, hemoglobin and red and white cell counts. No differences were seen in any group as compared with normal physiologic limits. On the last day of exposure, dams were autopsied and the following variables evaluated: liver weight, kidney weight, urinary albumin and chloride, number of corpora lutea, sites of implantation, post-implantation deaths and the number of live fetuses and their weights. Pre-

implantation deaths were defined as the difference between the number of corpora lutea and the number of implantation sites. The kidney weights of both mice and rats treated with chloroprene and ammonia were greater than controls ($P=0.01$ and 0.05, respectively). Liver weights in mice treated with chloroprene and ammonia were also increased relative to controls ($P=0.01$). In mice, the number of post-implantation deaths was significantly elevated ($P<0.001$) as compared with ammonia or air treated controls; rats were not affected. Incidence of rat fetuses with hematomas or cyanoses was elevated in the chloroprene and ammonia-exposed group, but not significantly ($P>0.05$). The mean number of normal rat fetuses/litter was decreased by 52% ($P<0.01$). The criteria for determining normal fetuses were not specified. Whether these effects might be attributable to a synergistic effect of ammonia and chloroprene is unclear. In addition, the amounts of oxidized chloroprene and other contaminants were not determined.

Salnikova and Fomenko (1973) exposed pregnant rats (22-30/group) to chloroprene via inhalation. Rats were exposed 4 hours/day throughout pregnancy to 1.11, 0.83, 0.17, 0.36 or 0.016 ppm chloroprene (purity not specified). The experiments were done at three different times, each with a concurrent control group (number not specified). Embryonic and fetal deaths were monitored. Fetuses were evaluated for the following: liver weight, femoral and fibular diaphysis lengths, and disturbances in vascular permeability. Two-month-old offspring from treated dams were examined for: urinary proteins, cholinesterase (tissue not specified), oxygen requirement, serum sulfhydryl content, urinary hippuric acid after benzoate loading, weight gain and weight ratios of brain, lungs, liver and kidneys. In dams exposed to 0.83 or 1.11 ppm chloroprene, embryonic deaths were significantly increased ($P<0.01$ and $P<0.05$, respectively). Exposure to 1 ppm chloroprene

resulted in depressed fetal body weight ($P<0.001$). Disturbances in vascular permeability and decreases in the lengths of the tibia and the fibula were also reported for exposure to 1 ppm chloroprene. Mortality in pups from dams exposed to 0.17 and 0.036 ppm chloroprene was significantly increased during the first 3 weeks postpartum ($P=0.05$ and $P<0.02$, respectively). A clear dose response was not seen in any of the physiological parameters measured in these offspring. Reporting of these data was variable and incomplete. NIOSH (1977) felt that interpretation of these data was not possible.

Apoiani (1970) examined the effect of chloroprene on pregnant rats housed at various distances from a chloroprene plant. The number of rats and length of exposure were not specified. In-plant chloroprene concentrations were reported to be as high as 61 ppm (Group 1). Mean chloroprene concentrations at distances from the plant of 500 meters (Group 2), 1500 meters (Group 3), and 7000 meters (Group 4) were 0.2, 0.14 and 0.05 ppm, respectively. Group 4 was used as the control. The authors noted increased fetal mortality (no specific data given), and reductions in placental weight. In Group 1, weights of fetal livers on day 20 of gestation were lower and gestation was lengthened. An increase in prenatal and neonatal deaths was also noted in this group. A non-dose related decrease in placental weights was noted for all exposed groups.

Salnikova and Fomenko (1973) studied the embryotoxic and teratogenic effects of chloroprene following both oral and inhalation exposures. Eight to 15 dams/group were evaluated. Six groups were given daily oral doses of 0.5 mg/kg. Each group was exposed for 2 consecutive days during gestation, through day 14 (i.e., day 3 and 4, day 5 and 6, etc.). One group was dosed every day from day 1 through 14. An unexposed control group was included.

Eight additional groups were exposed to 1.1 ppm chloroprene via inhalation, also for 2-day periods through day 18. The number of hours/exposure was not specified. All dams were sacrificed on day 20 of gestation. In the group of rats exposed to oral chloroprene for 14 consecutive days, embryonic deaths were significantly elevated ($P<0.001$). The number of embryonic and fetal deaths was also elevated in groups exposed on days 3 and 4 and on days 11 and 12 of gestation. All fetuses from the group exposed for 14 days showed hydrocephalus and internal bleeding. Embryonic and fetal deaths were elevated in litters from dams exposed via inhalation on days 1 and 2, 3 and 4, 9 and 10, 11 and 12, and continuously on days 1 through 20. An increase in hydrocephalus with cerebral herniation was seen in litters of dams exposed after day 5 of gestation, with the highest frequency in litters from dams exposed on days 5 and 6.

It is impossible to evaluate the significance of the Soviet teratology studies. Data on the purity of the compound to which the animals were exposed are lacking. In view of the purported differences in toxicity of pure chloroprene versus oxidation products, this becomes a serious problem. Incomplete reporting of experimental methodology and data creates other problems, especially since primary effects noted included embryo and fetal toxicity as opposed to frank terata. Data on maternal toxicity were not reported in many instances. The non-specific effects noted in the embryos and fetuses could have been a consequence of maternal toxicity. In addition, the negative teratology study of Culik et al. (1978) does not clearly indicate whether the highest dose employed was close to the maximum tolerated dose (MTD). As teratogenic effects may occur within a very narrow exposure window, this could also be a problem. In conclusion, insufficient data are available to adequately assess the teratogenic potential of chloroprene.

5.4. OTHER REPRODUCTIVE EFFECTS

5.4.1. Human Studies. Sanotskii (1976) reported disturbances in spermatogenesis in chloroprene workers after 6-10 years of exposure, and morphological sperm abnormalities after 11 years of exposure. He also reported an increase in spontaneous abortions in wives of these workers 3 times the incidence in the general population. Chloroprene concentrations within the plant ranged from 1-7 mg/m^3, with ammonia being the most frequently encountered agent to which the workers were exposed.

5.4.2. Animal Studies. von Oettingen et al. (1936) noted regressive changes in the spermatic epithelium or seminiferous tubules in rats exposed to a mean chloroprene concentration of 0.2 mg/ℓ (0.1-0.35 mg/ℓ) via inhalation. Two rats and four mice were exposed continuously for 35 days, two rats and three mice for 74 days, and four rats and four mice for 91 days. The testicular changes were noted in each of the groups of rats; similar effects were not seen in mice. Rats, mice and cats autopsied following lethal subcutaneous doses also showed pathological changes in the testes. Rats autopsied following lethal oral doses showed testicular pathology. The same kinds of effects were noted in rats exposed dermally to chloroprene. In this study segment, 0.5 cc of chloroprene was rubbed into the skin daily for 1 week. The animals were rested for 2 weeks, the hair removed, and 1.5 cc of chloroprene applied to the skin daily. Seven rats were treated for 55 days, and one for 49 days. At autopsy, the testes showed degeneration and calcification.

Male rats exposed to chloroprene by skin painting (amount not specified) for 33 or 44 days were mated to untreated females (6 males/group). In males treated for 34 days, breeding was delayed. Half of the animals exposed for 44 days failed to reproduce within 97 days. Male rats were exposed via

inhalation to the following concentrations (mg/ℓ): 0.434 (2 rats), 1.074 (1 rat), 1.088 (3 rats), 1.095 (1 rat), 2.223 (1 rat), 6.035 (12 rats), 8.421 (2 rats), 10.0 (3 rats), 16.983 (3 rats) and 22.419 (1 rat). All exposures were of 8 hours duration. Only 6 of these 19 animals successfully impregnated females, and in three of these, mating was delayed. The response was not dose dependent. All of six control males mated successfully. In similar experiments with mice, the same kinds of effects were reported.

Sanotskii (1976) noted that male rats exposed to chloroprene at a concentration of 1.69 mg/m³ for 4.5 months showed a reduction in the number of normal spermatogonia, an increase in the number of dead spermatozoa, a decreased period of sperm motility, and an increase in sensitivity to sperm inactivation in acid media. Exposure to 0.15 mg/m³ resulted in similar but less severe effects. Exposure to 0.051 mg/m³ caused no changes in spermatogenesis.

Culik et al. (1978) evaluated the effects of inhalation exposure on male reproductive function, in which 5 rats/dose were exposed to 0 or 25 ppm chloroprene 4 hours/day for 22 days. After the final exposure, each male was caged with three unexposed females. The males remained with the females for 7 days, after which they were transferred to a new group of females. This was repeated for 8 weeks. Litters of pups from these matings were evaluated for number of pups and body weight of pups at weaning. The percentage of successful matings, the percentage of pups surviving until 4 days postpartum, and the percentage of pups surviving until weaning were also monitored. No treatment related effects were found.

In mice, exposure to 3.5 mg/m³ for 2 months (eight animals) resulted in an increase in the number of "tubules with disquamating germinal epithelium." Exposure to 0.32 mg/m³ (seven animals) had no effect on testicular

morphology. A control group of eight animals was included. No effects on spermatogenesis were noted in mice (Sanotskii, 1976).

Pregnant rats were more sensitive to inhalation of 4 mg/m³ chloroprene (duration not specified) than were non-pregnant animals. Pregnant animals showed inhibition of spontaneous locomotor activity, an increase in urinary hippuric acid after sodium benzoate administration, hypoproteinemia, an increase in oxygen consumption, reduced weight gain and an increase in weight coefficients of brain, lungs, liver and kidneys. Non-pregnant animals showed a reduction in activity without the other effects. Exposure of pregnant animals to 0.6 mg/m³ resulted in hypoproteinemia; exposure to 0.013 mg/m³ had no effect on pregnant rats (Sanotskii, 1976).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

5.5.1. Effects in Humans. Avakian et al. (1960) reported on the health of 273 workers with 7-13 years of industrial chloroprene exposure (air concentrations not reported). Disorders of the cardiovascular system were the problems of primary concern. Fifteen percent of the workers noted heaviness in the chest, 48% had slow pulse, 19% had fast pulse, 6.7% showed signs of cardiac neurosis and 15-30% were hypotensive. Capillary permeability was found to be increased in the majority of the workers. Of 96 workers examined, 27% had decreased heart rates, 33% showed indications of myocardial dystrophy, and 15% showed atherosclerosis of the cardiac vessels. The control group (number not specific) showed a 7.3% incidence of myocardial dystrophy and 4.8% atherosclerosis. Follow-up examinations showed an increase to 39.2% of the workers showing signs of myocardial dystrophy and 39.2% cardiac neurosis.

Mikaelian and Frangulian (1965) reported that chloroprene depressed the immune response in exposed workers. Kechek and Semerdzhian (1972) reported

an increase in the β-globulin fraction and a decrease in the γ-globulin fraction of serum from chloroprene-exposed workers (air concentration not reported).

Mkhitarian (1960a,b) studied chloroprene workers from 1950-1954; 114 workers were included. Five different professions with varying degrees of chloroprene exposure were identified (actual exposure not reported); 25 workers had >10 years of exposure, 20 for 5-10 years and 33-37 for <5 years. Blood samples were tested for glucose, cholesterol, total protein, albumin, total globulins, glutathione, fibrinogen, carbonic anhydrase, catalase, calcium chloride and reserve alkalinity. Blood pressure was also measured. The following effects were reported: hypoglycemia, hypocholinesteremia, decreased carbonic anhydrase activity, decreased reserve alkalinity, hypotension and decreased blood clotting. Control data were not presented and statistical analyses were not performed.

Mnatsakanian and Mushegian (1964) studied porphyrin metabolism in children attending schools at various distances from a chloroprene plant. Schools were located at distances of 100, 500 and 700 meters from the plant, and air chloroprene concentrations were 0.08-0.13, 0.07-0.12 and 0.04-0.05 ppm, respectively. Urinary total coproporphyrin was measured in 42 children from the first school, 99 from the second and 105 from the third. Mean coproporphyrin levels were 6.36, 5.51 and 4.11 μg, respectively. NIOSH (1977) points out that all of these values fall well within normal values reported for children.

Mnatsakanian (1966) also measured urinary 17-ketosteroids as an indicator of adrenal function using the same groups of children. The control group had a mean value of 0.73 mg. Air chloroprene concentrations of 0.07-0.12 and 0.08-0.13 ppm corresponded to urinary 17-ketosteroid excretion

values of 0.0919 and 1.021 mg, respectively. NIOSH (1977) notes that both of these values are within the normal range for children.

Volkova et al. (1976) examined 65 chloroprene exposed workers; 43 had <5 years of exposure and 15 had worked from 10-20 years. Air chloroprene concentrations varied from 0.8-1.95 ppm. Workers complained of fatigue, headache and chest pain; 47% of the women reported menstrual disorders (10% in the control population, total number not specified). There was concomittant exposure to other substances.

Gasparian and Arutiunian (1965) did electroencephalographic examinations of 70 chloroprene production workers. Twenty non-exposed individuals were used as controls. Workers were primarily those with 5-15 years of exposure. The three most common types of EEG abnormalities were deflections of low voltage and frequency, deflections of low frequency but long duration (Δ-type), and inconsistent wave patterns with alternating α, β and Δ activities and occasional spikes. When the exposed workers were subjected to a flashing light, 82.8% responded, while 17.2% failed to respond; 100% of the control group responded. Of the exposed group, 78.6% did not synchronize with the frequency of a visual stimulus, while only 25% of the controls failed to synchronize. NIOSH (1977) notes that the original paper did not report many important experimental details.

Gooch and Hawn (1981) studied several groups of workers employed in a chloroprene plant. Workers were assigned to groups of currently exposed, previously exposed, and never exposed. Each job category was then rated as having a potential for high, moderate, low or varied exposure. Each worker had been subjected to a physical examination upon initial employment, and annually thereafter. The following serum evaluations were done: calcium,

phosphorus, glucose, blood urea nitrogen, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, lactic dehydrogenase and serum glutamic oxaloacetic transaminase. Whole blood was evaluated for white and differential cell counts, red blood cell count, hemoglobin and hematocrit.

The currently-exposed study group consisted of 336 workers, the not currently exposed group consisted of 227 workers, and the never-exposed group consisted of 283 workers. The never-exposed group were of plant workers with job categories in which direct exposure to chloroprene was not anticipated and was used as the control group for comparisons with the other two groups. Measurements of air chloroprene concentrations were not done, and it is uncertain how much indirect exposure these individuals might have had. In the currently-exposed group, 76 workers were selected for paired comparisons of test results before and after exposure to chloroprene. Why this procedure was not done with a larger percentage of the currentlyexposed group is not clear. Mean ages were comparable for the three groups. Sex composition varied; the currently-exposed group was 3.3% female, the not currently exposed group was 3.1% female, and the never-exposed group was 13.2% female. In the currently exposed group, 176 individuals had been exposed for <1 year, 80 for 1-5 years, 17 for 6-10 years and 63 for >10 years.

After adjustment of the data for age differences, no statistically significant effects ($P<0.05$) were found when biochemical parameters for the three groups were compared. In the group of 76 workers which served as their own controls, significant differences were found between baseline and postexposure values of cholesterol, glucose and LDH. The authors indicated that values both before and after exposure were within "normal" ranges, and

attributed the apparent effects to intrapersonal variability, rather than to chloroprene exposure. It is impossible to evaluate this study in reference to other occupational exposure evaluations which suggest effects in workers, since exposure data are not reported.

5.5.2. Effects in Experimental Animals. Rats exposed to chloroprene via inhalation (1.69 mg/m³) for 4.5 months showed an increase in the "summation index" (method not specified), a decrease in the synthesis of hippuric acid from sodium benzoate, and an inhibition of gas exchange. Exposure to chloroprene concentrations of 0.51 or 0.051 mg/m³ had no effect on these parameters. Using the same indicators, mice exposed to 35, 1.85, 0.32, 0.13, 0.064 and 0.054 mg/m³ showed no adverse effects. Apparently, mice were exposed for only 2 months (Sanotskii, 1976).

Clary et al. (1978) exposed rats to air concentrations of 39, 161 or 625 ppm chloroprene, and hamsters to 39, 162 or 630 ppm chloroprene for 4 weeks. Animals were exposed 6 hours/day, 5 days/week. Ten animals/sex/dose were used, with an equal size control group. In both rats and hamsters exposed to the highest levels, eye irritation, restlessness, lethargy, nasal discharge and orange-colored urine were noted. Hair loss was observed in female rats at the high and mid-exposure concentrations. Exposure-related growth retardation was observed. Food consumption was decreased in rats of both sexes during the early part of the study (not monitored in hamsters). In rats, no deaths were observed at the low dose; at the mid-dose, three males died during the course of the study (two after the first week, one after the second); and at the highest exposure level, five males and three females died during the course of the study. In hamsters, there were no deaths at the low dose; one male and three females died during the course of the mid-dose exposure; and at the highest exposure concentration, all

animals died within the first week. There were no deaths in the control groups. After 4 weeks of exposure, blood samples were evaluated for hemoglobin, packed cell volume, erythrocytes and white blood cells. No treatment related effects were seen. In addition to body weight, weights of heart, kidney, liver, spleen, brain, thyroid and adrenals were recorded. In rats of both sexes, body weights were significantly depressed at all exposure levels. No differences were seen in heart or spleen weights. In females, kidney weights were elevated at both the mid and high doses; brain weights were increased at all dose levels; lung, thyroid and adrenal weights were increased at the high dose. In male rats, heart weights were unaffected; liver weights were depressed at the low and mid-dose and elevated at the high dose; spleen weights were decreased at all dose levels; brain weights were higher in all dose groups; lung weights were elevated at the highest exposure level; and adrenal weights were increased in all exposed groups.

Nystrom (1948) exposed 10 rats to an air chloroprene concentration of 56 ppm, every day for 8 hours/day for 5 months. There were no deaths, nor changes in body weight, red cell counts, leukocyte counts or hemoglobin levels. "Inconsiderable" changes were observed at autopsy.

Asmangulian and Badalian (1971) exposed rats (number unspecified) to daily oral doses of 15 mg/kg for 5 months. No deaths were reported and no information on other indicators of toxicity was presented. A comparative biochemical study on the effects of chloroprene ingested in water on enzyme systems and the reproductive function of male rats was reported by Krasovsky et al. (1979). When chloroprene was given in concentrations at the level of 0.1 mg/ℓ, β-galactosidase in the liver and blood gonadal inosine diphosphatase significantly increased while the time during which spermatozoa

remained motile decreased. However, the original article is in Russian and funds or time were not available for translation. The effects are observed at much lower doses than others.

5.6. ACUTE TOXICITY

5.6.1. Effects in Humans. The effects of acute exposure to high concentrations of chloroprene include central nervous system depression, lung injury, liver and kidney damage, irritation of the skin and mucous membranes, respiratory difficulties, dermatitis and alopecia (IARC, 1979).

Roubal (1942) reported the following effects in workers from the Czechoslovakian chloroprene rubber industry: hair loss, chest pressure, rapid pulse, severe fatigue, conjunctivitis, necrosis of the corneal epithelium and albumin in the urine.

Nystrom (1948) reported the results of medical evaluation of Swedish chloroprene workers. Experimental exposure of human subjects to 973 ppm chloroprene resulted in nausea and giddiness after 15 minutes in resting subjects, and 5-10 minutes in subjects performing light work. Pilot plant workers exposed to 459 ppm chloroprene were anemic. In the main plant, chloroprene concentrations ranged from 56 to >334 ppm. Workers developed extreme fatigue and severe chest pains after 1 month of work. They also reported personality changes including irritability. Contact dermatitis and hair loss were also reported. Liver, kidney and lung function tests, and electrocardiograms were normal.

Lejhancova (1967) evaluated six women exposed to chloroprene. Chloroprene concentrations ranged from 61-292 mg/m^3. The women reported headaches, nausea and severe fatigue, as well as hair loss.

Paulet and Malasses (1969) reported a high frequency of chemical burns in workers employed in a French polychloroprene plant. Conjunctivitis, hair loss and sexual impotency were also reported.

5.6.2. Effects in Experimental Animals. von Oettingen et al. (1936) evaluated the pathological consequences of single oral lethal doses of chloroprene in rats. Doses varied from 0.2-0.8 mℓ chloroprene. None of the three animals dosed with 0.2 mℓ chloroprene died; 100% of the animals dosed with 0.8 mℓ chloroprene (four animals) died, with time of death varying from 6 hours to 10 days after dosing. A dose of 0.3 mℓ (five animals) resulted in 40% mortality within 4 days. Animals showed inflammation of the mucous membranes, particularly of the eyes and nose, and irritation of the gastrointestinal tract. At autopsy, the lungs were hyperemic, showing edema and hemorrhagic areas. The liver, spleen and kidneys were hyperemic, and the livers were frequently enlarged.

A more recent study reported that fasted rats were exposed to concentrations of 100, 150, 225 and 300 ppm chloroprene for 4 hours and killed at 24 hours (Plugge and Jaeger, 1979). Liver injury was measured by increased serum sorbitol dehydrogenase (SDH) activity and was apparent in animals exposed to 225 and 300 ppm chloroprene. Non-protein sulfhydryl (NPSH) concentrations in liver were increased 24 hours after all exposures. These authors further reported that lung NPSH concentrations were decreased significantly after 100- and 300-ppm exposure and that serum lactate dehydrogenase (LDH) activity was increased after exposure to 300 ppm. When this same enzyme was measured in lung lavage fluid from animals killed 24 hours after exposure, no elevation was detected. Thus, acute lung injury did not manifest itself with a release of LDH into the airway at this time. Alternatively, airway injury may have resolved by 24 hours.

Mice were exposed to chloroprene via inhalation for 1 hour to 1-33 mg/ℓ chloroprene. A concentration of 1 mg/ℓ did not result in any fatalities in nine animals. All concentrations >3 mg/ℓ resulted in 100%

mortality at varying time intervals after exposures. The lungs showed edema, emphysema and hemorrhagic areas. In addition, the liver, spleen and kidneys were hyperemic (von Oettingen, 1936).

Table 5-1 presents acute toxicity data for chloroprene.

TABLE 5-1

Acute Toxicity of Chloroprene*

Exposure Duration	Species	Exposure Concentration or Dose	Effect
1 hour inhalation	3000 mg/m³	mouse	LC_{50}
2 hour inhalation	2300 mg/m³	mouse	LC_{50}
4 hour inhalation	360 mg/m³	rat	Single liver and lung enzyme changes
4 hour inhalation	540 mg/m³	rat	Single liver and lung enzyme changes
4 hour inhalation	810 mg/m³	rat	Multiple liver and lung enzyme changes
4 hour inhalation	1080 mg/m³	rat	Multiple liver and lung enzyme changes
8 hour inhalation	600 mg/m³	mouse	LC_{50}
8 hour inhalation	1300 mg/m³	cat	LC_{50}
8 hour inhalation	3400 mg/m³	rabbit	LC_{50}
1 subcutaneous dose	3 mg/kg	mouse	LD_{50}
1 oral dose	25 mg/kg	rat	LD_{50}
1 oral dose	260 mg/kg	mouse	LD_{50}

*Source: Sanotskii, 1976

6. AQUATIC TOXICITY

6.1. ACUTE

Pertinent data regarding the acute effects of chloroprene toxicity were not located in the available literature.

6.2. CHRONIC

Pertinent data regarding the chronic effects of chloroprene toxicity were not located in the available literature.

6.3. PLANT EFFECTS

Pertinent data regarding the plant effects of chloroprene were not located in the available literature.

6.4. RESIDUE

Pertinent data regarding residue of chloroprene were not located in the available literature. Veith et al. (1980) have suggested, however, the use of the following equation to estimate bioconcentration factor (BCF):

$$\log BCF = 0.76 \log K_{ow} - 0.23$$

where K_{ow} is the octanol-water partition coefficient. Using this equation and the estimated log K_{ow} of 1.78 from Section 1, the BCF for whole fish is calculated to be ~13. Therefore, significant bioconcentration of chloroprene is not expected.

6.5. OTHER RELEVANT INFORMATION

Pertinent data regarding other relevant information on chloroprene were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

The ACGIH recommended Threshold Limit Value (TLV) is 10 ppm (ACGIH, 1980). This recommendation is based primarily upon an unpublished study showing growth retardation in rats and hamsters exposed to 50 ppm chloroprene via inhalation for 2 years or 18 months, and upon "minimal" toxicity observed in rats and hamsters following 4-week inhalation exposures to 39 ppm chloroprene.

NIOSH (1977) recommends a 15-minute ceiling concentration of 1 ppm as a workplace standard. This lower recommended limit reflects consideration of Soviet animal and epidemiological data showing mutagenic and reproductive effects following low level exposures.

Other occupational exposure recommendations include: West Germany, 10 ppm; Sweden, 25 ppm; Romania, 8 ppm; East Germany, 3 ppm; and Russia, 0.6 ppm (ACGIH, 1980).

8. APPROACHES TO RISK ASSESSMENT

The data base for chloroprene is both conflicting and incomplete. Russian investigations tend to show adverse effects at lower inhaled doses than other studies, but generally do not report experimental methods necessary for comparisons. Adequate dose-response data after oral chloroprene exposure are lacking.

Both human and animal data, however, indicate that mutagenicity, as measured by chromosomal aberrations, dominant lethal mutations (in animals), and an increase in spontaneous abortions (human), as well as adverse effects on male reproductive capacity, are the most sensitive indicators of chloroprene toxicity (Table 8-1). Soviet workers have demonstrated these effects in experimental animals at very low levels. Interpretation of these data are difficult, as mentioned. Workers in other countries have demonstrated similar effects only at much higher doses. The Soviet studies do not report experimental methodology in adequate detail, especially in terms of the purity of the compound administered. Since there are indications that oxidation products of chloroprene may be much more toxic than the monomer per se, this becomes a serious consideration. The Russian epidemiological studies are bracketed with the same concern. In addition, although chromosomal aberrations certainly generate concern, their ultimate significance in terms of the consequences to exposed individuals and subsequent generations remains unclear. Animal data do indicate that chloroprene is a potential mutagen to germ cells as well as somatic cells. Available data are inadequate to assess the potential carcinogenicity of chloroprene.

NIOSH (1977) took all of these data and associated problems into consideration when an occupational exposure limit of 3.6 mg/m^3 was suggested. For the purposes of this assessment, it is recommended that the NIOSH (1977)

TABLE 8-1

Summary of *In Vivo* Mutagenicity and Reproductive Effects

Species	Route	Concentration	Effect
human	inhalation	18 mg/m³	Chromosome aberrations
human	inhalation	6 mg/m³	Chromosome aberrations
human	inhalation	1-7 mg/m³	Chromosome aberrations
human	inhalation	2-2.2 mg/m³	Chromosome aberrations
mouse	inhalation	1.85 mg/m³	Dominant lethal mutations
rat	inhalation	0.14 mg/m³	Dominant lethal mutations
mouse	inhalation	0.13 mg/m³	Chromosome aberrations
rat	inhalation	90 mg/m³	Pregnant females exposed; no effect on offspring
rat	inhalation	3.0 mg/m³	Embryotoxic
rat	oral	0.5 mg/kg	Embryotoxic, teratogenic
rat	inhalation	3.98 mg/m³	Embryotoxic, teratogenic
human	inhalation	1-7 mg/m³	Effects on spermatogenesis and sperm morphology; increase in spontaneous abortions
rat	inhalation	200 mg/m³	Abnormal testicular morphology
mouse	inhalation	0.32 mg/m³	Abormal testicular morphology
rat	inhalation	0.15 mg/m³	Decreased sperm viability, motility
rat	inhalation	90 mg/m³	Males exposed; no effects on reproductive performance observed

guideline be used as a starting point for development of a criterion level. Such a procedure is consistent with guidelines previously published (45 FR 79354, 1980).

Assuming an 8-hour breathing volume of 10 m^3, an absorption efficiency of 50% and spreading exposure out over 7 days, the calculated intake would be:

$$3.6\ mg/m^3 \times 10\ m^3 \times 0.5 \times 5/7 = 12.86\ mg/day$$

An estimated acceptable daily intake (ADI) of 0.13 mg/day for a 70 kg man is calculated by applying an uncertainty factor of 100. This factor represents 10 in order to protect potentially more sensitive segments of the general population, and 10 for both the uncertainty associated with the choice of 3.6 mg/m^3 as a inhalation NOAEL (no-observed-adverse-effect level) whereas data are available to indicate that this dose may be associated with adverse effects (see Table 8-1) and the uncertainty inherent in the extrapolation from the inhalation to the oral route of exposure.

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